May 20, 2003

Christine Todd Whitman, Administrator
U.S. Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Ave., N.W.
Washington, DC 20460

Subject: Comments on the HPV Test Plan for Acetonitrile, 2,2',2",2"'-(1-ethane-diyldinitrilo) tetrakis

Dear Administrator Whitman:

The following comments on Akzo Nobel's High Production Volume Challenge test plan for the chemical Acetonitrile, 2,2',2",2"'-(1-ethane-diyldinitrilo) tetrakis, known as EDTN, are submitted on behalf of the Physicians Committee for Responsible Medicine, People for the Ethical Treatment of Animals, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These health, animal protection, and environmental organizations have a combined membership of more than ten million Americans.

Akzo Nobel Functional Chemicals LLC submitted its test plan on January 24, 2003 and is a producer of the chemical EDTN (CAS No. 5766-67-6), which is then transported to one location within the US and exported to two additional sites. EDTN is an intermediate in the production of EDTA and is identified as a closed system intermediate. EDTA is a common laboratory reagent used in laboratories worldwide.

In the absence of experimental data for EDTN, the chemical structure, physical/chemical properties, and metabolism of a structurally similar chemical, PDTN, were examined in the test plan. This approach is consistent with the EPA's stated goals of maximizing the use of existing data in order to limit additional animal testing. Also, we agree with Akzo Nobel in its analysis of the available toxicity data. Furthermore, we concur in the identification of EDTN as a closed system intermediate, making it exempt from sub-chronic or reproductive toxicity testing.

At this time, however, we question Akzo Nobel's assessment that a developmental toxicity study (OECD 414) is needed to meet the requirements of the HPV program. This test was proposed because there were no developmental toxicity data available to meet this SIDS requirement.

According to Akzo Nobel, worker exposure is low, as EDTN exists in the form of a wet cake. As indicated in the test plan (p. 4), plant operators also wear masks and gloves, further reducing any potential exposure. In addition, existing acute rat oral and dermal toxicity testing show a **very low order of toxicity** in rodents (LD50 values for PDTN (>2000mg/kg) as do existing repeat dose NOAEL data for PDTN (200 mg/kg/day). Due

to similarities of the two chemicals, PDTN animal data has been used to extrapolate to EDTN to meet the SIDS requirements for mammalian toxicity studies. In terms of the HPV program, "read-across" analysis should be used to decrease in animal testing.

In spite of this, Akzo Nobel proposes additional tests on animals without adequately recognizing the lack of exposure of workers to EDTN. The proposed developmental toxicity test (OECD 414) will cause the suffering and deaths of either 900 rabbits or 1300 rats. Towards the same goal, a combined repeated dose/reproductive/developmental toxicity test (OECD 422) could be conducted with the use of a fewer number of animals, 675 rats rather than the proposed 900 rabbits or 1300 rats. The fact that Akzo Nobel plans to conduct the developmental toxicity test that harms the largest number of animals shows a disregard for reducing the number of animals killed in this program. And, the results will neither affect how EDTN is handled nor result in further limits on worker exposure and risks since these are already controlled with worker protective measures.

Conducting this test clearly violates Sections 1 and 8 of the HPV agreement and the EPA December 2000 *Federal Register* notice that states 1. "In analyzing the adequacy of data, participants shall conduct a thoughtful, qualitative analysis rather than use a rote checklist approach. Participants may conclude that there are sufficient data, given the totality of what is known about a chemical, including **human experience**, that certain endpoints need not be tested" and 2. "As with all chemicals, before generating new information, participants should further consider whether any additional information obtained would be useful or relevant." The exposure and risk to EDTN are already well controlled, making further testing of this compound wasteful, unnecessary, and cruel. In reviewing past HPV test plans, i.e. Rosin Adducts and Adducts Salts, Rosin Esters, Trixylenyl Phosphate, submitted by Akzo Nobel or through Pine Chemicals Association (PCA), it was noted that 1) inappropriate animal tests were proposed despite the availability of *in vitro* tests to address HPV/SIDS hazard endpoints, 2) existing data were not always fully utilized, and 3) there was a lack of thoughtful toxicology, e.g., proposing aquatic testing on insoluble materials, etc. As discussed above, we feel there are elements of this plan which follow this unfortunate tradition and do not fully implement the October 1999 letter agreement.

If Akzo Nobel insists on investigating the potential developmental toxicity for EDTN, we strongly urge it to consider an *in vitro* method, in order to spare large numbers of animals. The rodent embryonic stem cell test, an *in vitro* embryotoxicity test method, has recently been validated by the European Centre for the Validation of Alternative Methods, and the Centre's Scientific Advisory Committee has concluded that this test is ready to be considered for regulatory purposes (Genschow 2002). If a positive result is found in the embryonic stem cell test, EDTN should be treated as a development toxicant/teratogen, and no further testing should then be carried out within this screening-level program. Although we have written to the EPA repeatedly concerning the inclusion of the embryonic stem cell test in the HPV Program, with correspondence dating back more than six months, we have received no reply. We urge Akzo Nobel Functional Chemicals LLC to correspond directly with the EPA on the incorporation of this validated non-animal test.

Summary:

Akzo Nobel and the end users of EDTN, a closed system intermediate, have long established good industrial hygiene practices to prevent exposure. Additional animal testing will not affect how EDTN is handled and used because: a) EDTN exists in the form of a wet cake, b) worker exposure is already limited from the use of good industrial hygiene practices, and c) EDTN has a very low order of toxicity based on "read-across" data for the related chemical, PDTN. Because of the well-known characteristics of this hazard, workers are already protected, and additional animal testing will not demonstrate need for additional steps to reduce worker exposure. The proposed animal studies are a waste of animals, time, and resources, and we advise Akzo Nobel to forego additional testing.

In-vitro tests are available to characterize developmental risks in a screening level program, and these should be conducted *in lieu* of the proposed *in vivo* tests. It is the stated goal of the EPA to incorporate *in vitro* methods into the HPV program as they become available and we ask that the EPA review this test plan with with regards to the October 1999 agreement and thoughtful toxicology to avoid a mere box checking exercise which results in killing additional animals.

I look forward to a prompt and favorable response to our concerns. I may be reached at 202-686-2210, ext. 327, or via e-mail at meven@pcrm.org.

Sincerely,

Megha Even, M.S.
Research Analyst

Chad B. Sandusky, Ph.D.
Director of Research

References:

Genschow, E., *et al.*, "The ECVAM international validation study on *in vitro* embryotoxicity tests: Results of the definitive phase and evaluation of prediction models", *Altern. Lab. Anim.* 30: 151-76, 2002.